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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/568,156	Arnold et al.,
Examiner	**Art Unit**
Frank Lu	1655

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Nov 22, 2000*.

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-3 and 8-24* is/are rejected.

7) ☒ Claim(s) *4-7* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Drawings

1. The drawings submitted on November 22 have been approved by the office.

Claim Rejections - 35 U.S.C. § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1, 2, 8, 11, 15, 16, 22, and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Bates *et al.*, (Nucleic Acids Res. 23, 3627-3632, 1995).

Bates *et al.*, teach detection and kinetic studies of triplex formation by oligodeoxynucleotides using real-time biomolecular interaction analysis (BIA). In this study, 5'-Biotinylated oligonucleotides were immobilized on the streptavidin-coated surface of a biosensor chip (page 3628, right column, first and second paragraphs) and subsequently hybridized to their complementary strand. Sequence-specific triplex formation was observed when a suitable third-strand oligopyrimidine was injected over the surface-bound duplex (page 3628, right column, last paragraph). In addition, a single-stranded oligonucleotide immobilized on the chip surface was able to capture a DNA duplex by triplex recognition. For example, Bt-T30 immobilized on the chip surface has been shown to capture of T30-A30 duplex (see second

paragraph of left column in page 3629, fourth paragraph of left column in page 3630, Figure 4 and Figure 2 for sequences of oligonucleotides).

Therefore, Bates *et al.*, teach all limitation cited in claims 1, 2, 8, 11, 15, 16, 22, and 23.

Response to Arguments

In page 6, last paragraph bridging to page 7, first paragraph of applicant's remarks, applicant argued that the structure requirement in the claims " is neither met nor suggested by the cited art, which relates to an entirely different kind of polynucleotide binding called Hoogsteen binding" since "there is no complementarity, as expressly required by our claims" in the cited art".

The arguments have been fully considered but it is not persuasive toward the withdrawal of the rejection because claims 1 and 15 do not require that the probe and target are complementary. Claim 1 only requires that double stranded probe or target comprises complementary strands and single stranded probe or target has a potential to be complementary with one of the complementary strands. "Complementarity" in claim 1 could be considered as "a potential to be complementary with one of the complementary strands".

Claim Rejections - 35 U.S.C. § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1, 2, 8-13, and 15-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tyagi *et al.*, (Nature Biotechnology 14, 303-308, March 1996) in view of Pease et al., (Proc. Natl. Acad. Sci. USA 91, 5022-5026, 1994).

Tyagi *et al.*, teach fluoresce upon hybridization using molecular beacons as probes (see page 304, Figure 1). These probes comprised covalently linked and non-covalently linked complementary strands with a hairpin structure as described in claims 8, 9, and 16-18 (page 304, Figure 2) and undergo a spontaneous fluorogenic conformational change when they hybridize to their targets (page 303, abstract). Note that one of molecular beacon probes (molecular beacon A) used in this study consists of a 15-nucleotide-long-probe sequence embedded within two complementary 5-nucleotide-long arm sequences and could be considered as a double strand probe. The fluorophore, EDANS is joined to the 5'-terminal phosphate by a $-(CH_2)_6-S-CH_2-CO-$ linker; and the quencher, DABCYL, is joined to the 39-terminal hybroxyl group by a $-(CH_2)_7-NH-$ linker. This prior art encompasses some embodiments/limitations of claims 1, 2, 8-10, and 15-22.

Tyagi *et al.*, do not disclose a microarray with different immobilized oligonucelotides as described in claims 1 and 15.

Pease *et al.*, teach do light-generated oligonucleotide arrays for rapid DNA sequence analysis. In a preliminary experiment, a 1.28 x 1.28 cm array of 256 different octanucleotides was produced and hybridized with fluorescently labeled oligonucleotide probes.

Therefore, in the absence of an unexpected result, it would have been obvious to one having ordinary skill in the art at the time the invention was made to have immobilized different stranded targets on a microarray as suggested by Pease *et al.*, and hybridized a single stranded target in the presence of a divalent cation using a probe with a structure of molecular beacons containing partial double strand region wherein complementary strands are both covalently and noncovalently linked as suggested by Tyagi *et al.*. One having ordinary skill in the art would have motivated to modify and combine above methods together because the effect of divalent cations in the stabilization of duplex DNA is well known in the art (see Boehringer Mannheim Biochemicals, Nonradioactive in Situ Hybridization Application Manual, Chapter III, page 1, right column) and simple replacement of one hybridization probe (a molecular beacon) from another hybridization probe (oligonucleotide) for a hybridization assay, in the absence of an unexpected result, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made. As regards the motivation to make the substitution cited above, the motivation to combine arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

6. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tyagi *et al.*, (Nature Biotechnology 14, 303-308, March 1996) in view of Anderson et al., (Nucleic Acid Hybridization: a practical approach, edited by Hames & Higgins, pages 86-109, 1985).

The teachings of Tyagi *et al.*, have been summarized previously, *supra.*

Tyagi *et al.*, do not disclose Northern blot and release of immobilized probe.

Anderson *et al.*, teach reuse of filters and probes after hybridization. A hairpin probe and RNA immobilized on a filter could be considered as a double stranded probe and polynucleotide target. Hybridized probe can be washed from the RNA filter (see page 109).

Therefore, in the absence of an unexpected result, it would have been obvious to one having ordinary skill in the art at the time the invention was made to perform Northern blot and release the immobilized probe from a solid support as suggested by Anderson *et al.*. One having ordinary skill in the art would have motivated to use different probes in Northern blot assay and reuse of hybridized filter after hybridization because simple replacement of one hybridization probe (a molecular beacon) from another hybridization probe (oligonucleotide) for a hybridization assay, in the absence of an unexpected result, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made. As regards the motivation to make the substitution cited above, the motivation to combine arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their

common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955)

7. Claims 14 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tyagi *et al.*, (Nature Biotechnology 14, 303-308, March 1996) in view of Pease et al., (Proc. Natl. Acad. Sci. USA 91, 5022-5026, 1994) and Brown *et al.*, (US Patent 5, 807, 522 , filed on June 7, 1995).

The teachings of Tyagi *et al.*, have been summarized previously, *supra.*

Tyagi *et al.*, do not disclose a microarray with different immobilized oligonucelotides as described in claims 1 and 15.

The teachings of Pease *et al.*, have been summarized previously, *supra.*

Pease *et al.*, do not disclose a microarray immobilized different oligonucelotides with a polycationic surface as described in claims 14 and 24.

Brown *et al.*, teach fabricating microarrays coated with a layer of poly-l-lysine (Sigma) with immobilized biological samples as described in claims 14 and 24. The microarrays were fabricated on microscope slides (column 16, lines 23 and 24). Poly-l-lysine coated glass slides could be obtained commercially, e.g., from Sigma Chemical Co. (St. Louis, Mo.) (column 13, last paragraph). As described in example 2, the cDNA clones were spotted on poly-l-lysine coated microscope slides. Total poly-A mRNA from wild type Arabidopsis was isolated using standard

methods (Maniatis, et al., 1989) and reverse transcribed into total cDNA, using a fluorescein nucleotide analog to label the cDNA product (green fluorescence). cDNA copies of mRNA from the transgenic plant were labeled with a lissamine nucleotide analog (red fluorescence). Two micrograms of the cDNA products from each type of plant were pooled together and hybridized to the cDNA clone array in a 10 microliter hybridization reaction (fifth and sixth paragraphs of column 17). Genes equally expressed in wild type and the transgenic Arabidopsis appeared yellow due to equal contributions of the green and red fluorescence to the final signal. The dots were different intensities of yellow indicating various levels of gene expression (second paragraph of column 18).

Therefore, in the absence of an unexpected result, it would have been obvious to one having ordinary skill in the art at the time the invention was made to have immobilized single stranded targets on a microarray comprised a polycationic surface as suggested by Pease *et al.*, and Brown *et al.*, and hybridized a single stranded target using a probe with a structure of molecular beacons containing partial double strand region wherein complementary strands are both covalently and noncovalently linked as suggested by Tyagi *et al.*. One having ordinary skill in the art would have motivated to modify and combine above methods together because simple replacement of single stranded targets (oligonucleotides) from double stranded targets (cDNAs) on a polycationic array, in the absence of an unexpected result, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made. As regards the motivation to make the substitution cited above, the motivation to combine arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when

combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955)

Response to Arguments

In page 7, second paragraph of applicant's remarks, applicant argued that: (1) the binding in Ellouze *et al.*, involves no complementarity; and (2) nowhere in the claims describes or suggests " the claimed solid phrase hybridization assay involving triplex formation by hybridization between complementary target and probes".

The arguments have been fully considered but it is not persuasive toward the withdrawal of the rejection because the motivation to combine cited reference is not based on triplex formation as applicant suggested.

Conclusion

8. Rejections found in the prior office action yet not restated herein above have been withdrawn.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Claims 4-7 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

11. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703) 308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (703) 305-1270. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the Chemical Matrix receptionist whose telephone number is (703) 308-0196.

Frank Lu
February 9, 2001

Ethan Whisenant, Ph.D.
Primary Examiner (FSA)